Conferences and Reviews

Hypoglycemias

F. JOHN SERVICE, MD, PhD, *Rochester, Minnesota*

Low concentrations of blood glucose were recognized as a feature of some diseases in the last century. However, it was not until insulin became available for the treatment of diabetes mellitus in the early 1920s that symptoms similar to those arising from overtreatment with insulin were observed in nondiabetic persons. This observation led to the postulation of a new disease entity called *hyperinsulinism.*[1] Support for the existence of hyperinsulinism was provided from the identification of a malignant pancreatic islet cell tumor in 1927 in a patient who had episodes of severe hypoglycemia.[2] Postmortem extracts of metastatic tissue caused marked hypoglycemia in rabbits. The first cure of hyperinsulinism resulted from the successful removal by Graham of an insulinoma in 1929.[3]

Consequent to the development of radioimmunoassay for insulin, hyperinsulinism was confirmed as the pathophysiologic basis for some but not all cases of hypoglycemia.

Physiology of Glucose Homeostasis

Hypoglycemic disorders arise from abnormalities in the mechanisms involved in glucose homeostasis. Unlike many physiologic functions that proceed at relatively steady rates, glucose homeostasis requires mechanisms to respond to the intermittent provision of exogenous nutrients and intervals of no nutrient supply. Processes for energy storage are activated during food ingestion, and those required to release stored energy operate during periods of food deprivation. The resultant effect on glycemia is that of a semidamped system in which plasma glucose is maintained between approximately 70 mg per dl and 180 mg per dl in healthy active persons through a balance between glucose production and glucose utilization.

Postprandial State

Postprandial plasma glucose concentrations are influenced by the size of a meal, its composition, and the time of day it is eaten.

Insulin is the chief modulator of glucose homeostasis (Table 1). The increased concentrations of glucose and various insulinotropic enteric factors following food ingestion stimulate insulin secretion. Insulin suppresses hepatic glucose production and stimulates glucose utilization. Estimates of the relative contributions of these two processes have varied depending on the techniques used for their measurements. Unlike the hepatic vein catheter technique, which measures only net differences across the splanchnic bed, the dual isotope method can estimate hepatic glucose production. Studies in which this technique was used have shown that ≥90% of ingested glucose reaches the peripheral circulation.[4] However, since hepatic glucose production is reduced by 60% to 70% postprandially, the net addition of glucose to the peripheral circulation is reduced by about 35%.[4] Elevated postprandial insulin concentrations (1) promote glycogen formation through the stimulation of glycogen synthetase and suppression of phosphorylase and (2) decrease the concentrations of gluconeogenic precursors, branched-chain amino acids, free fatty acids, and ketone bodies. Suppression of glucose production and inhibition of glycogenolysis are more sensitive to increases in insulin concentration than are stimulation of glucose utilization and inhibition of gluconeogenesis. Following the ingestion of 100 g of glucose, about 10 g of hepatic glycogen is formed by direct uptake of glucose and 10 to 15 g is formed by gluconeogenesis.

Although glucagon is an important glucoregulatory hormone in the postabsorptive state, its role in nutrient disposition postprandially has not been clearly elucidated.

Pari passu with the diminishing absorption of glucose from the intestinal tract and the predominance of glucose utilization over glucose production late postprandially, the plasma glucose concentration falls. Concomitantly the plasma insulin concentration decreases. The waning effect of insulin restores glucose utilization and production to preprandial rates. At this point there is a transition from a state of glucose storage to one of carefully husbanded glucose production at rates that satisfy the obligatory requirements of the glucose-dependent tissues.

Postabsorptive State

About 4 to 6 hours after food ingestion, plasma glucose concentrations are 80 to 90 mg per dl and rates of glucose utilization and production are approximately 2 mg per kg per min. Glucose production is primarily (70% to 80%) from hepatic glycogenolysis, with a lesser contribution (20% to 25%) from hepatic gluconeogenesis.[5] After an overnight fast, the liver contains 40 to 50 g of glucose in the form of glycogen. On the assumption that there is an obligatory rate of glucose utilization of 1 to 1.5 mg per kg per min, glycogen stores should be depleted after 24 to 36 hours of fasting. In the postabsorptive state glucagon stimulates glucose production by enhancing glycogenolysis and gluconeogenesis and by inhibiting glycolysis (Table 1). Glucagon activates glycogen phosphorylase and inactivates glycogen synthetase. Glucagon has no known direct effect on extrahepatic glucose uptake. Basal concentrations of catecholamines do not appear to influence glucose homeostasis in the postabsorptive

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From the Department of Internal Medicine, Division of Endocrinology, Mayo Clinic. Dr Service is Professor of Medicine, Mayo Medical School, Rochester, Minnesota.
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Reprint requests to F. John Service, MD, PhD, Department of Internal Medicine, Division of Endocrinology, Mayo Clinic, Rochester, MN 55905.

state. Cortisol seems to have a permissive effect on glucose metabolism. Its presence is needed for normal glycogen synthesis and for the acceleration of glucose production by glucagon and epinephrine (Table 1). Cortisol antagonizes the actions of insulin and thereby accelerates gluconeogenesis, lipolysis, ketogenesis, and proteolysis and decreases glucose utilization. The hyperglycemic effect of cortisol is not immediate but delayed by two hours. Cortisol decreases both hepatic and extrahepatic sensitivity to insulin.[6]

Glycogenolysis

Glycogen, a polymer of glucose, serves as a reservoir for glucose. Although glycogen is stored in both the liver and skeletal muscle, only the liver and kidney possess the enzymes capable of yielding free glucose. In muscle, glycogen breakdown yields lactate, which, after transport to the liver, may enter the gluconeogenic pathway (Figure 1). Glycogenolysis involves the activity of several enzymes. Phosphorylase, which is stimulated by glucagon and epinephrine but inhibited by insulin, cleaves glycogen, to liberate glucose-1-phosphate, at alpha 1 to 4 linkages up to within 3 to 5 glycosyl units of a 1,6 branch point. After oligo 1,4–1,6-glycan transferase (a debrancher), which splits the 1,6 linkages, has acted, phosphorylase activity can continue. Amylo-1,6-glucosidase releases free glucose. Phosphoglucomutase converts glucose-1-phosphate to glucose-6-phosphate, which can be hydrolyzed to free glucose by glucose-6-phosphatase. Since the latter enzyme is present only in the liver and kidney, only these organs can provide free glucose. Deficiency of glucose-6-phosphatase results in severe hypoglycemia; deficiencies of phosphorylase and debrancher enzymes cause mild degrees of hypoglycemia.[7]

TABLE 1.—*Hormonal Control of Glucose Homeostasis*

Hormone	*Hepatic Glucose Production*	*Extrahepatic Glucose Utilization*	*Basal Glucose Production*	*Relative Importance to Recovery From Insulin-Induced Hypoglycemia*
Insulin	↓	↑	↓	...
Glucagon	↑	–	↑	+++
Catecholamines*	↑	↓	–	+
Cortisol	↑	↓	↑	–
Growth hormone†	↑	↓	–	–

↑ = increase, ↓ = decrease, – = no effect

*Epinephrine is approximately 10 times more potent than norepinephrine. Its action is primarily through a β-adrenergic mechanism. In the presence of glucagon deficiency, catecholamines make a modest contribution to the recovery from hypoglycemia.
†Have an acute and transient hypoglycemic effect.
From Service FJ: Hypoglycemic disorders. In Wyngaarden JB, Smith LH (Eds): Cecil Textbook of Medicine, 18th Ed. Philadelphia, WB Saunders Company, 1988, pp 1381-1387.

Approximately half of the glucose utilized (1 mg per kg per min) is committed to the obligatory noninsulin-mediated uptake of glucose by the brain.[8] As plasma glucose in patients with insulinomas reached concentrations at the threshold level for the occurrence of symptoms of hypoglycemia, glucose utilization rates were 1.3 mg per kg per min.[9]

In the postabsorptive state the daily glucose consumption by a person weighing 70 kg is approximately 30 g by muscle, 120 g by brain, 34 g by blood elements, and 2 g by the renal medulla.

Fasting State

After several days of food deprivation, plasma glucose concentrations fall to 45 to 60 mg per dl; these levels can be maintained for several weeks. Rates of glucose utilization

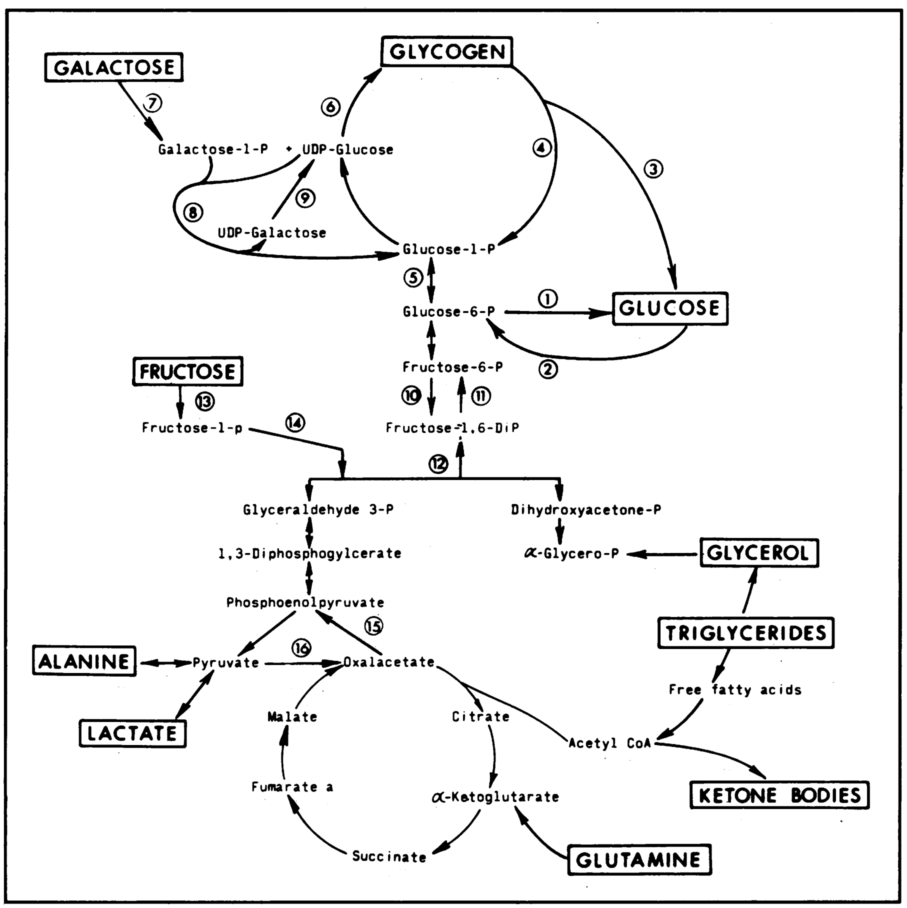

Figure 1.—Metabolic pathways involved in glycogen synthesis and degradation and gluconeogenesis. Key enzymes are designated by number. (1) glucose 6-phosphatase, (2) glucokinase, (3) amylo-1,6-glucosidase, (4) phosphorylase, (5) phosphoglucomutase, (6) glycogen synthetase, (7) galactokinase, (8) galactose 1-phosphate uridyl transferase, (9) uridine diphosphogalactose-4-epimerase, (10) phosphofructokinase, (11) fructose 1,6-diphosphatase, (12) fructose 1,6-diphosphate aldolase, (13) fructokinase, (14) fructose 1-phosphate aldolase, (15) phosphoenolpyruvate carboxykinase, (16) pyruvate carboxylase. (Modified from Pagliara AS, et al: Hypoglycemia in infancy and childhood. Part I. J Pediatr 1973; 82:365, with permission.)

decrease to approximately 1 mg per kg per min and remain constant thereafter. During this period, plasma free fatty acid and ketone body concentrations increase; these substances serve as energy sources for muscle. Furthermore, ketone bodies replace glucose as the predominant fuel for neural tissues, thereby reducing the obligatory glucose uptake by the brain.[10] Women tolerate food deprivation less well than do men.

Gluconeogenesis

Gluconeogenesis is the process by which new glucose is synthesized from noncarbohydrate precursors. Since this process sustains glucose production after glycogen depletion, hypoglycemia arising from defective gluconeogenesis should be evident only after prolonged food deprivation. Lactate, pyruvate, glycerol, and amino acids are the major gluconeogenic substrates. Because not all glycolytic enzymes have reversible activity, another series of enzymes—pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose-1,6-diphosphatase, and glucose-6-phosphatase—is required to effect the conversion of gluconeogenic substrates to free glucose (Figure 1). The relative contributions to gluconeogenesis of various substrates are: lactate and pyruvate 60%, glycerol 13%, and amino acids 29%.[5] Substrate availability can be an important modulator of gluconeogenesis, since the concentrations of these precursors in the postabsorptive state are below those necessary for maximal rates of gluconeogenesis. Lactate is derived primarily from erythrocytes, skeletal muscle, brain, and skin. Adipose tissue is the source of glycerol. Skeletal muscle is the chief source of alanine and glutamine, the most important amino acid substrates for gluconeogenesis. Alanine is derived largely from the transamination of pyruvate from branched-chain amino acids (leucine, isoleucine, and valine), which act as nitrogen donors. Branched-chain amino acids may account for as much as 60% of alanine nitrogen. The importance of amino acids for glucose homeostasis during fasting is illustrated by the occurrence of hypoglycemia when alanine availability is reduced because of the impairment of leucine metabolism in maple syrup urine disease.[11]

Gluconeogenesis from alanine is increased by 100% after 48 hours of fasting. With more prolonged food deprivation the contribution of alanine to gluconeogenesis decreases. In contrast, plasma lactate concentration does not wane during prolonged starvation, and its contribution to gluconeogenesis remains constant at 50% above postabsorptive levels. After 30 hours of fasting, differences among men, women, and children have been observed in gluconeogenic substrates. Children had the lowest plasma glucose and alanine and highest beta-hydroxybutyrate concentrations, with those in men being the obverse and those in women being intermediate. After 86 hours of fasting, leucine, valine, and isoleucine concentrations increase, whereas levels of aspartate, threonine, serine, proline, glycine, alanine, methionine, tyrosine, phenylalanine, and glutamine remain essentially unchanged.[12]

Even in the presence of adequate gluconeogenic precursors, gluconeogenesis may be inhibited by an alteration in the cellular redox state, the effect of which is to inhibit gluconeogenic enzymes—e.g., alcohol hypoglycemia. The metabolism of ethanol results in an increase in $NADH/NAD^+$ ratio with an attendant decrease in the conversion of lactate, alanine, and glycerol to glucose. Hypoglycemia may occur following ingestion of the unripe ackee fruit through the interference with gluconeogenesis by the inhibition of pyruvate carboxylase and fatty acid oxidation.[13]

Mechanisms of Recovery From Hypoglycemia

Coincident with the recovery phase of acute hypoglycemia are marked increases in concentrations of plasma, glucagon, and epinephrine (Table 1). Increases in plasma concentrations of cortisol and growth hormone occur later. When permissive amounts of cortisol and growth hormone are present, further increases in their concentrations are not necessary for recovery from hypoglycemia. Acute increases in plasma concentrations of growth hormone decrease plasma glucose whereas more prolonged increases cause hyperglycemia. The latter effect is mediated by decreasing glucose utilization and stimulating glucose production through an action antagonistic to insulin. In contrast, glucagon is essential for normal recovery from hypoglycemia.[14] Catecholamines do not appear to be essential for recovery from hypoglycemia as long as glucagon secretion is intact.[14] However, catecholamines are necessary for recovery from hypoglycemia in the presence of glucagon deficiency[14] or when hypoglycemia is profound (Figure 2).

Catecholamines increase glucose production directly by stimulating both glycogenolysis and gluconeogenesis and indirectly by stimulating glucagon release (Table 1). Epinephrine also decreases glucose utilization by directly inhibiting tissue glucose uptake and by inhibiting insulin release. Epinephrine is approximately 10 times more potent than norepinephrine in producing these effects. Epinephrine stimulates glucose production directly by a beta-adrenergic mechanism and indirectly by inhibiting insulin secretion by an alpha-adrenergic mechanism. Glucose counterregulation from insulin-induced hypoglycemia is primarily by glycogenolysis during the first two hours and then from gluconeogenesis thereafter (Figure 3).[15]

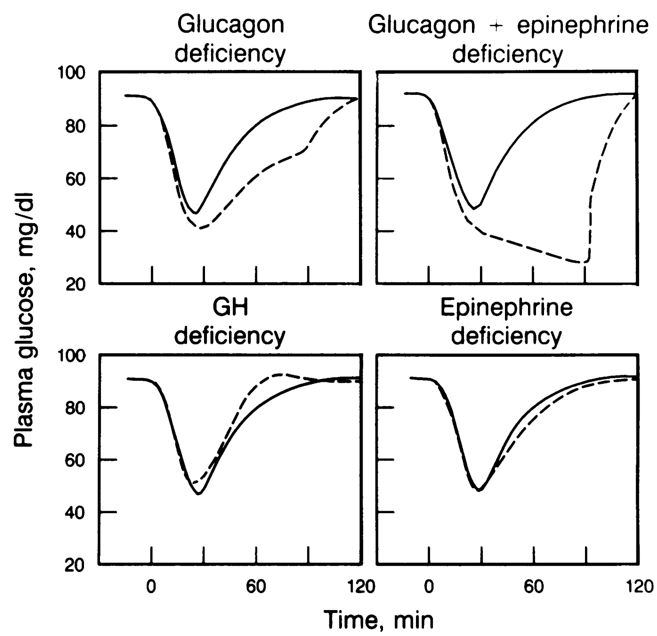

Figure 2.—Plasma glucose curves during insulin-induced hypoglycemia in man with counterregulation intact (solid lines) and during selective blockade of counterregulatory hormones (dashed lines). (Modified from Cryer, et al: Roles of glucagon and epinephrine in hypoglycemic and nonhypoglycemic glucose counterregulation in humans. Am J Physiol 1984; 247 [Endocrinol Metab 10]:E198, with permission.)

Classification of Hypoglycemic Disorders

Hypoglycemic disorders may be classified in several different ways. A classification may separate disorders on the basis of a biochemical characteristic, e.g., hyperinsulinemia, or on the basis of pathophysiologic behavior, e.g., rates of glucose production and utilization. Categorization of hypoglycemic disorders by insulin concentration is less than ideal because some disorders mediated by insulin-like action are not associated with hyperinsulinemia. In addition, hypoglycemic disorders do not segregate easily by rates of glucose turnover, viz., those due to overutilization of glucose and those due to underproduction of glucose. Hypoglycemia cannot be generated unless the rate of glucose utilization exceeds that of glucose production. Insulinoma, the condition anticipated to be the quintessential model of excessive glucose utilization, has been found to be associated with lower than normal rates of glucose utilization and production[9] (Figure 4). To date, a hypoglycemic disorder entirely due to excessive glucose utilization in the face of normal glucose production has not been confirmed by isotopic assessments of rates of glucose turnover. However, large amounts of glucose have been required to control hypoglycemia in patients with non-islet cell tumor[16] and in patients with malnutrition.[17] Considering the paucity of data on glucose flux rates in hypoglycemic states, classification by this criterion seems unwarranted. Since patients primarily manifest clinical features, an expeditious classification may be one related to clinical presentation (Figure 5).

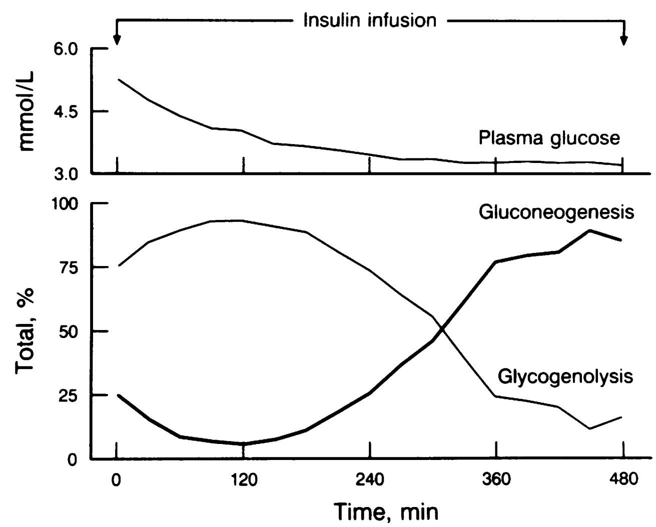

Figure 3.—Time course of contributions of gluconeogenesis and glycogenolysis to overall hepatic glucose output during glucose counterregulation against insulin-induced hypoglycemia in healthy subjects. (Modified from Lecavalier L, et al: Contributions of gluconeogenesis and glycogenolysis during glucose counterregulation in normal humans. Am J Physiol 1989; 256 [Endocrinol Metab 19]:E844.)

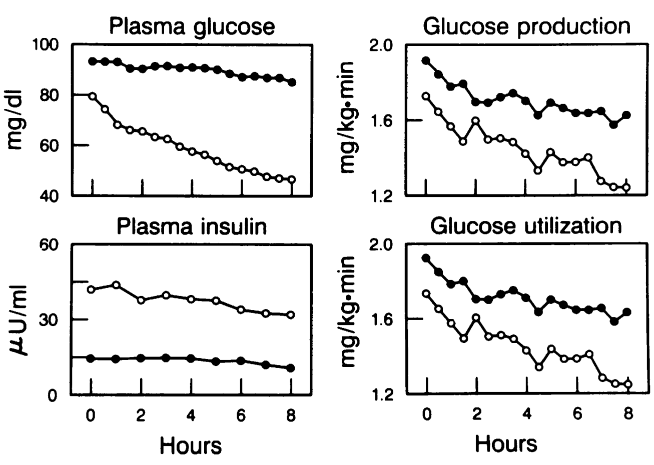

Figure 4.—Plasma glucose and insulin levels and rates of glucose production and utilization in 6 insulinoma patients and 8 normal subjects during an 8-hour fast. (Modified from Rizza RA, et al: Pathogenesis of hypoglycemia in insulinoma patients. Diabetes 1981; 30:377, with permission.)

Clinical Evaluation

Defects of many of the mechanisms that maintain plasma glucose in the normal range are associated with readily recognizable clinical syndromes. In some instances the symptoms and signs of the primary disorder predominate over those of hypoglycemia or at least point to the existence of the primary disorder. In some patients with such conditions as multisystem disease, poor nutrition, and multiple drug use, the basis for hypoglycemia may be uncertain and the patient too ill to undergo extensive evaluation.

In the majority of patients with symptoms of hypoglycemia who appear healthy, screening laboratory tests should include plasma glucose, insulin, calcium, phosphate, uric acid, lipids, creatinine, insulin antibodies, cortisol, and liver function. Documentation of drug-induced hypoglycemia may be difficult. A detailed history must be obtained, and every medication, including nonprescription drugs, used by the patient must be examined.

When a patient is observed with symptoms of hypoglycemia, 10 to 20 ml of blood in addition to that for glucose determination should be withdrawn. The specific analyses to be done on the saved specimen can be determined by clues generated from the history and physical examination. Such an opportunity may provide sufficient data to establish the cause of the hypoglycemic disorder or at least narrow the diagnostic possibilities. Glucose or glucagon should be administered following blood withdrawal to any patient suspected of being hypoglycemic. Prompt treatment will shorten the duration of hypoglycemia, and, if the patient is not hypoglycemic, no harm will be done.

In patients with asymptomatic hypoglycemia one must be alert for artifactual hypoglycemia. Whole blood glucose values may be spuriously low in polycythemia vera because of the unequal distribution of glucose between erythrocytes and plasma or excessive glycolysis by erythrocytes, or both. Low blood glucose values in leukemia are due to excessive glycolysis by leukocytes and in hemolytic crisis from excessive glycolysis by nucleated erythrocytes. In the polycythemic patient or in serum of the leukemic or hemolytic patient, prompt measurement of glucose in plasma to which an antiglycolytic agent has been added should provide accurate results.

An uncommon and challenging problem is the low plasma glucose concentration in an asymptomatic patient in whom laboratory error and spurious result have been ruled out. Such patients may have adapted to long-standing hypoglycemia or have mild symptoms that have been unrecognized.

A flow diagram of a clinical approach to the evaluation of a suspected hypoglycemic disorder is presented in Figure 5. Note that the evaluation is directed to patients who appear healthy. For those who do not appear healthy the results of the history and physical examination will determine the direction of the investigation.

Hypoglycemic disorders cause a constellation of symptoms that usually recur as discrete episodes at irregular intervals. A useful but not infallible historical aid is the timing of symptoms in relation to food intake: those occurring within four hours of food intake are due to the food-stimulated hypoglycemias and those occurring beyond five hours of food intake are due to the food-deprived hypoglycemias.

Considerable effort should be expended to obtain from the patient and family members a detailed description of symptoms and careful attention paid to their occurrence in relation to food intake (Figure 6). Symptoms may result from activation of the autonomic nervous system (sweating, shakiness, anxiety, palpitations, and weakness) or impairment of central nervous system function (reduced intellectual capacity, confusion, irritability, abnormal behavior, convulsions, and coma). Hypothermia may be an accompaniment. Sometimes the autonomic symptoms that precede the central nervous system symptoms go unrecognized. Symptoms of hypoglycemia usually occur at plasma glucose concentrations of about 45 mg per dl or less (whole blood glucose of 40 mg per dl or less).[18] Although some studies suggest that a rapid fall in glucose concentration results in symptoms even when plasma glucose does not decrease below 45 mg per dl, the weight of evidence does not support this relationship.[19]

The symptoms of hypoglycemia are nonspecific. For this reason it is necessary to demonstrate a low plasma glucose value concomitant with symptoms and subsequent relief of symptoms by correction of the hypoglycemia, i.e., *Whipple's triad.*[20] This triad should be demonstrated before hypoglycemia can be considered to be the basis for a patient's symptoms. Although food—especially free carbohydrate—will relieve symptoms regardless of the cause of the hypoglycemia, persons without a hypoglycemic disorder may feel better after eating. It is, therefore, imperative to confirm that symptoms are due to biochemically confirmed low glucose concentration. The tests available for evaluation of patients with a hypoglycemic disorder are meal test, intravenous tolbutamide test, C-peptide suppression test, and intravenous glucagon test (postabsorptive and/or when hypoglycemic) and prolonged supervised fast. For those food-deprived hypoglycemias associated with elevated plasma insulin levels, measurement of plasma C-peptide permits a determination to ascertain whether the hyperinsulinemia is endogenous or exogenous in origin (Figure 7).

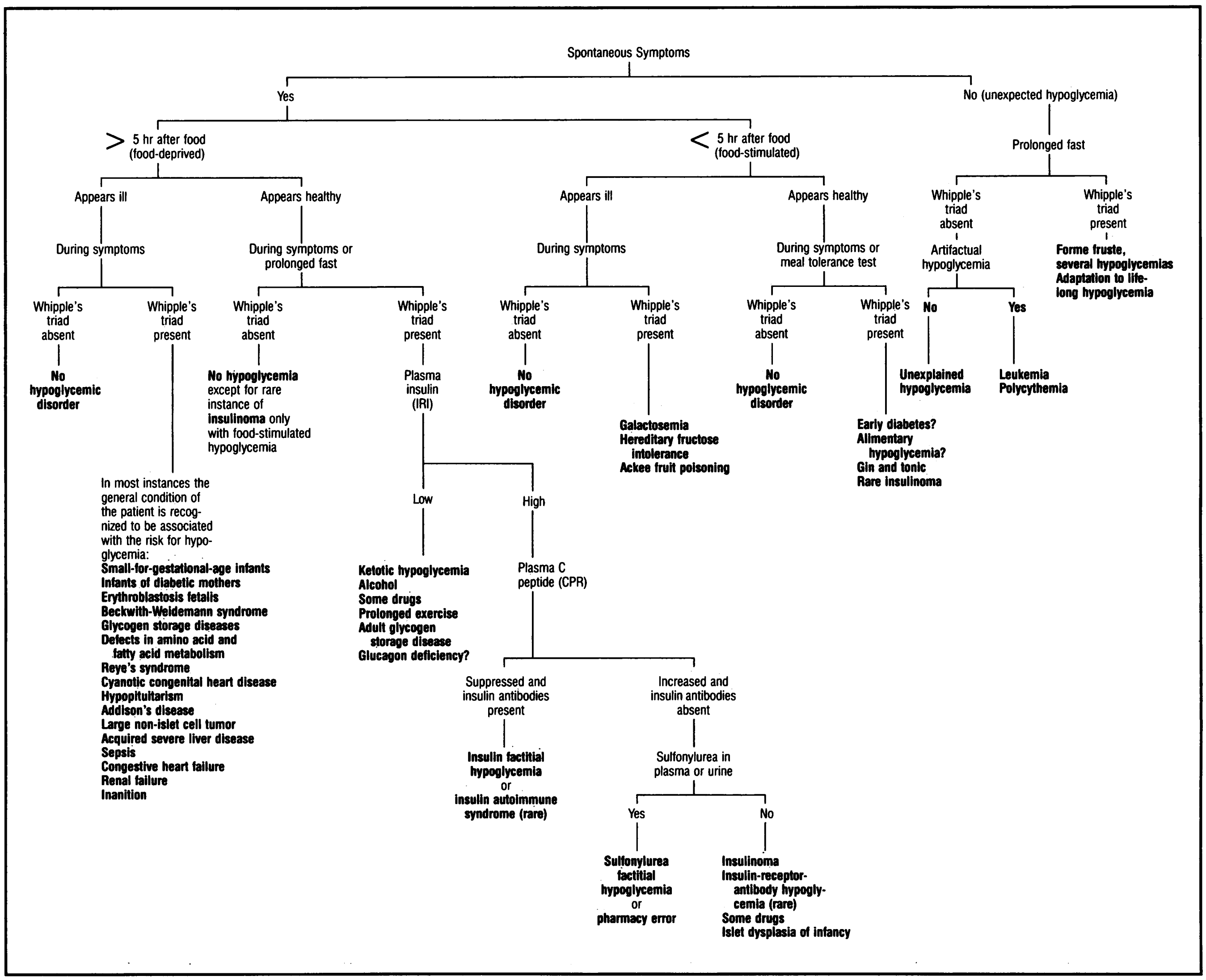

Figure 5.—Evaluation of hypoglycemic disorders. (Modified from Service FJ: Hypoglycemic disorders, *In* Wyngaarden JB, Smith LH Jr (Eds): Cecil Textbook of Medicine, 18th Ed. Philadelphia, WB Saunders Company, 1988, pp 1381-1387.)

Food-stimulated Hypoglycemias

Subsequent to the conceptualization of hyperinsulinism, many patients with postprandial symptoms of the autonomic type were found to have normal concomitant blood sugar concentrations. For such cases the term functional hyperinsulinism was coined.[21] Eventually, reliance on a subnormal glucose concentration at the time of spontaneous symptoms came to be replaced by the oral glucose tolerance test.[22] Reproduction of postprandial symptoms experienced in daily activities during the oral glucose tolerance test associated with a plasma glucose nadir ≤50 mg per dl (or its equivalent) has been considered confirmation of the presence of a food-stimulated hypoglycemic disorder.[23] Use of the oral glucose tolerance test is fraught with risk of misdiagnosis, since (1) at least 10% of healthy persons have plasma glucose nadirs <50 mg per dl;[23,24] (2) there is no correlation between the nadir of plasma glucose concentrations and the occurrence of autonomic symptoms;[25] and (3) the results of oral glucose tolerance tests are variable upon repeated testing.[26] Plasma cortisol responses, rates of glucose descent, hypoglycemic indices, and plasma epinephrine responses—all of which have been recommended to improve the accuracy of the oral glucose tolerance test—have failed to do so or have not been assessed during placebo oral glucose tolerance tests. In fact, many patients with postprandial autonomic symptoms experience symptoms after a "placebo" oral glucose tolerance test.[24]

Patients with postprandial autonomic symptoms generally have been classifiable into one of three categories: those with normal oral glucose tolerance tests (functional hypoglycemia); those who have undergone surgical modification of the upper gastrointestinal tract (alimentary hypoglycemia), and those with elevated one- and two-hour glucose levels in an oral glucose tolerance test (early diabetes hypoglycemia). The incidence of hypoglycemia postprandially in patients after gastric surgery varies from 5% to 37%. Alimentary hypoglycemia has been reported in patients who have undergone a variety of surgical procedures (gastrectomy, gastroenterostomy, vagotomy, and pyloroplasty) and in some with intact GI tracts and is characterized by symptoms of hypoglycemia two hours postprandially. This phenomenon should be distinguished from the dumping syndrome, which may cause similar symptoms but occurs within an hour of eating, is unassociated with hypoglycemia, and is presumed to be caused by contraction of the plasma volume due to fluid shift into the gastrointestinal tract. Although plasma glucose nadirs ≤50 mg per dl during oral glucose tolerance testing in patients who have undergone these surgical procedures are not uncommon, hypoglycemic symptoms are much less frequently seen.[27]

Of 101 patients considered to have early diabetes with a blood glucose of <50 mg per dl at the fourth or fifth hour after an oral glucose load, <5% had had symptoms of hypoglycemia after meals.[28] No correlation has been found between the presence of symptoms of hypoglycemia postprandially during ordinary life and the severity of the hypoglycemia during the oral glucose tolerance test, regardless of subtype.

Unfortunately, the basis for the postprandial symptoms is

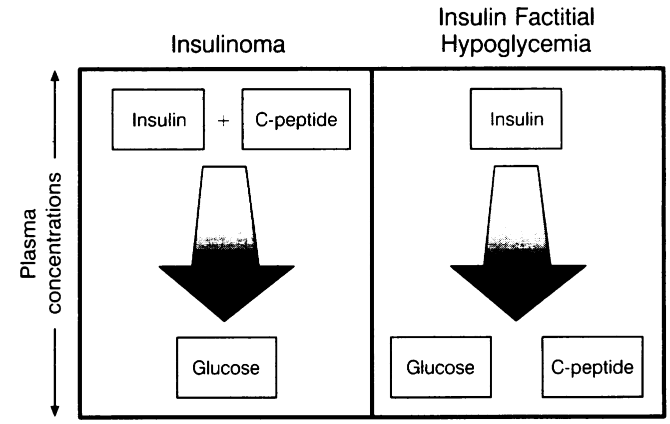

Figure 7.—Endogenous hyperinsulinemia from insulinoma is associated with elevated C-peptide concentrations with concurrent hypoglycemia. Exogenous hyperinsulinemia from injected insulin results in low concentrations of C-peptide both because of the effect of the associated hypoglycemia and because of the direct suppressive effect of insulin on the pancreatic beta cell. (Modified from Service FJ: Hypoglycemic disorders, *In* Wyngaarten JB, Smith LH Jr (Eds): Cecil Textbook of Medicine, 18th Ed. Philadelphia, WB Saunders Company, 1988, pp 1381-1387.)

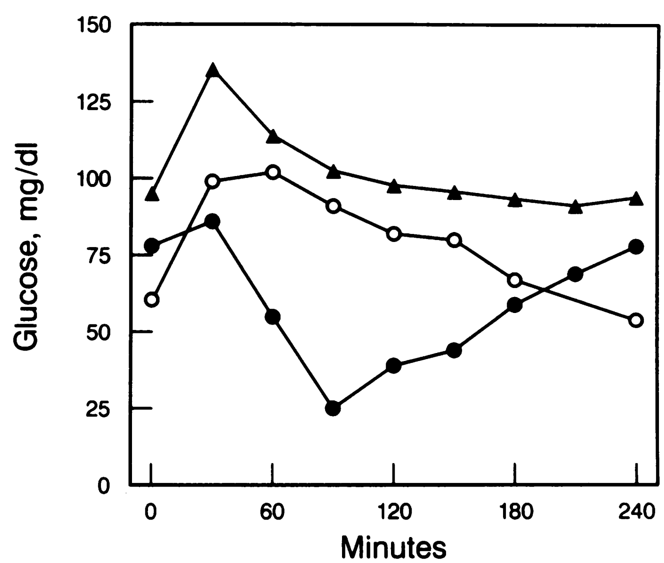

Figure 6.—Differential plasma glucose responses to a mixed meal between food-stimulated hypoglycemia (closed circle) and food-deprived hypoglycemia (open circle) in contrast to healthy subjects (triangle).

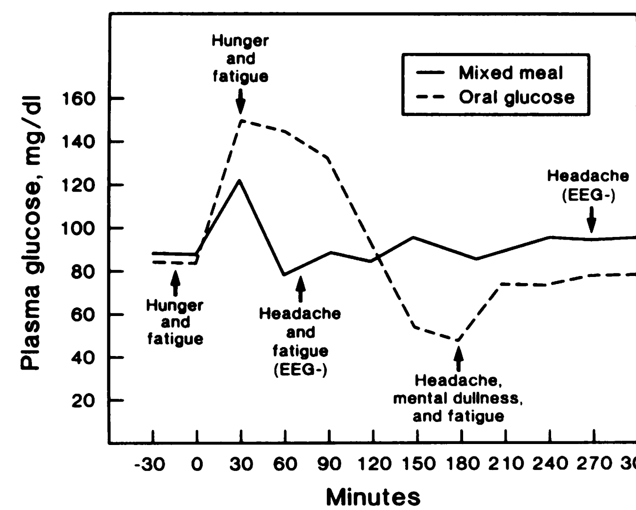

Figure 8.—Plasma glucose responses to oral glucose tolerance test contrasted to responses to a mixed meal in patients with postprandial symptoms suggestive of food-stimulated hypoglycemia. Despite symptoms during both tests, no EEG abnormalities were found.

obscure in patients in most published reports because glucose concentrations usually were never measured during spontaneous symptoms. In one study in which patients collected capillary blood on filter paper at the time when postprandial symptoms were present, centrally measured blood glucose levels were almost invariably not in the hypoglycemic range.[29]

When plasma glucose responses to a mixed meal were compared with those following an oral glucose tolerance test, none of the patients who had a hypoglycemic nadir after oral glucose evinced hypoglycemia after the mixed meal or any EEG evidence of hypoglycemia[30] despite the occurrence of symptoms during both tests (Figure 8). Therefore, the oral glucose tolerance test should not be used for the evaluation of hypoglycemia in patients with symptoms in the postprandial period. Instead, plasma glucose should be measured during the spontaneous occurrence of symptoms or after ingestion of a meal typical of that followed by symptoms.[29]

Unfortunately, reliance on the oral glucose tolerance test for the diagnosis of food-stimulated hypoglycemia has led to extensive publications not on disorders of hypoglycemia but on the oral glucose tolerance test. Most persons with autonomic symptoms following meals have been shown to have psychoneurosis.[25] The use of low-carbohydrate/high-protein or high-fiber diets, sulfonylureas, biguanides, and anticholinergic agents for the treatment of food-stimulated hypoglycemias has only limited scientific support. Hypoglycemia following the ingestion of substances that are toxic to susceptible persons may be considered in the category of food-stimulated hypoglycemias, e.g., in children with galactosemia and hereditary fructose intolerance.

The ingestion of large amounts (equivalent to three highballs) of ethanol and simple carbohydrate (gin and tonic) but not complex carbohydrate may cause hypoglycemia within three to four hours in some healthy persons.

The unripe ackee fruit may result in hypoglycemia in children and adults with chronic malnutrition.[13]

Food-deprived Hypoglycemias

Drug-induced Hypoglycemias

Drugs constitute the most common cause of hypoglycemia when insulin and sulfonylurea treatments of diabetic persons are included.[31] Factors that increase the risk for drug-induced hypoglycemia are extremes of age, antecedent food deprivation, and impaired renal and hepatic function. Salicylates may cause hypoglycemia in children.[31] Propranolol has been implicated as a contributor to hypoglycemia in patients with other potentially hypoglycemia-provoking conditions.[31] Other drugs recently reported to cause hypoglycemia are disopyramide (Norpace), sulfamethoxazole and trimethoprim (Bactrim, Septra) in the presence of renal failure, pentamidine (Lomidine), and quinine when used for cerebral malaria. Since a wide variety of drugs has been implicated as the cause of hypoglycemia, the reader is referred to review articles on this subject.[31] Ethanol-induced hypoglycemia arises from inhibition of gluconeogenesis as a result of the increase in the NADH/NAD$^+$ ratio in instances of depleted hepatic glycogen.[32] The increased NADH/NAD$^+$ ratio suppresses the conversions of lactate to pyruvate, alpha-glycerophosphate to dihydroxyacetone phosphate, and glutamate to alpha-ketoglutarate and several tricarboxylic cycle reactions. Infusion of ethanol into healthy subjects for four hours was observed to result in hypoglycemia; reduced rates of hepatic glucose production; suppressed plasma insulin concentrations; increased plasma lactate, beta-hydroxybutyrate, glycerol, and free fatty acid concentrations; and increased lactate/pyruvate and beta-hydroxybutyrate/acetoacetate ratios.[33] Hypoglycemia usually develops within 6 to 36 hours of the ingestion of even moderate amounts of ethanol by persons chronically malnourished or by healthy persons who have missed one or two meals. Children, even though healthy, are especially susceptible to ethanol-induced hypoglycemia. Blood alcohol levels may not be elevated when the patient is hypoglycemic.

Hypoglycemia Due to Insulinoma

Approximately 60% of patients with insulinoma are female.[34] Insulinomas are uncommon in persons younger than 20 years of age and rare in those younger than 5 years. The median age at diagnosis is about 50, except in patients with the multiple endocrine neoplasia (MEN) syndrome, in which it is in the mid-20s.[34] Ten percent of patients with insulinoma are older than 70 years of age.[34]

Of patients with insulinoma, 80% have single benign tumors, 11% have multiple benign tumors, 6% have single malignant tumors, and the remainder have multiple malignant tumors or islet hyperplasia.[34] Ten percent of insulinoma patients have MEN syndrome type I, and 80% of these patients have multiple insulinomas. The commonest associated endocrine abnormality is primary hyperparathyroidism; pituitary tumors appear in approximately 50% of the patients.[34] Only 60% of patients with multiple insulinomas have the MEN syndrome.[34]

Some tumors secrete hormones in addition to insulin: gastrin, 5-hydroxyindoles, ACTH, glucagon, and somatostatin. In rare instances, insulinomas have occurred in non-insulin-dependent diabetic persons[35] but have never been documented in an insulin-dependent subject. Insulinomas have been successfully removed from pregnant women.[34]

Clinical Picture. Symptoms may be present for as short a time as one week and as long as many years before the diagnosis. The longest duration of confirmed hypoglycemic episodes has been 23 years.[36] In a series of 95 patients with insulinomas, 85% of patients had various combinations of

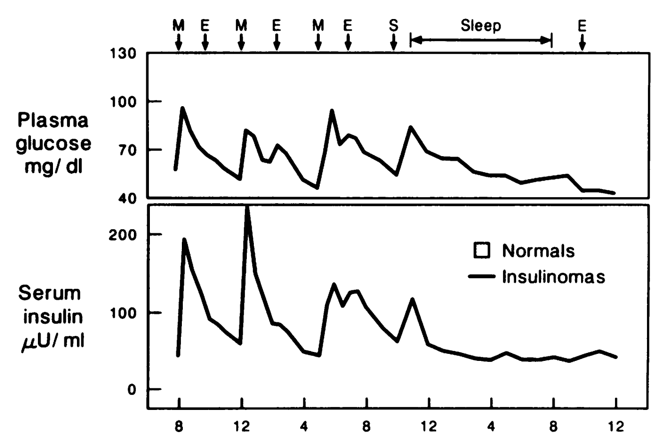

Figure 9.—Serial measurements of plasma glucose and serum insulin in patients with insulinoma and healthy subjects under ordinary life conditions. Plasma glucose declined to hypoglycemic levels in the late postabsorptive and fasting states in those with insulinoma. Hyperinsulinemia was observed in response to meals and also in the postabsorptive and fasting states. (M = meal; S = snack; E = exercise) (Modified from Service FJ and Nelson RL: Insulinoma. Compr Ther 1980; 2:70, with permission.)

diplopia, blurred vision, sweating, palpitations, and weakness; 80% had confusion or abnormal behavior; 53% had unconsciousness or amnesia; and 12% had grand mal seizures.[34] Twenty percent of cases may be misdiagnosed, the belief being that the patient has a neurologic or psychiatric disorder.[34]

Hypoglycemia usually occurs several hours after a meal, most commonly before the evening meal[18] (Figure 9). In rare instances, symptoms may occur solely in the postprandial period rather than during fasting.[34] Symptoms may be aggravated by exercise, alcohol use, a high protein-low carbohydrate diet, treatment with sulfonylureas, and religious fasts.[34] Less than 20% of patients with insulinoma gain weight.[18] Hypoglycemic peripheral neuropathy has been observed in rare cases of insulinoma.[37]

Diagnosis. The diagnosis of insulinoma is based on the demonstration of Whipple's triad and hyperinsulinemia (or an inappropriately "normal" insulin level for a low glucose value). Although insulin antibodies are usually undetectable,[34] in rare instances minimal titers of insulin antibodies in patients with surgically proved insulinoma have been noted. Useful outpatient diagnostic tests are the intravenous tolbutamide (IVTT) and C-peptide suppression tests. These tests should not be performed unless the fasting plasma glucose is known to exceed 50 mg per dl before the test. (Concern about the safety of the IVTT is based on two reports of serious side effects. However, in those reports tolbutamide was injected when patients were already significantly hypoglycemic.) When it is verified that the preinjection plasma glucose is ≥50 mg per dl, no adverse effects have been observed.[38] The IVTT should not be performed in anyone who has been food-deprived for several days (e.g., immediately after a 72-hour fast), in anyone with poor nutrition, or in patients with severe liver disease. Neither test should be conducted in a patient with hypopituitarism or hypoadrenocorticism who has not taken the morning dose of replacement glucocorticoid.[34]

The criterion that provides the best accuracy for diagnosis is to average the plasma glucose values at 120, 150, and 180 minutes after tolbutamide administration (Figure 10). If the mean value at these time points is less than 55 mg per dl for lean persons and 62 mg per dl for obese persons there is a high likelihood (>95 sensitivity with 95% specificity) that the patient has an insulinoma. There is less accuracy for diagnosis by using the ratio of the plasma glucose at 180 minutes after tolbutamide to the fasting value or by examination of the plasma insulin responses. If the plasma glucose responses to intravenous tolbutamide are normal, the insulin values should be ignored.[34,38] The C-peptide suppression test is based on the observation that hypoglycemia induced by exogenous insulin fails to suppress C-peptide concentration normally in those with insulinomas[39] (Figure 11). The criteria for normal C-peptide suppression will depend on the C-peptide assay. The euglycemic C-peptide suppression test involves maintenance of euglycemia during insulin infusion. This approach relies on inhibition of insulin release by insulin and has the advantage of avoiding hypoglycemia. It is difficult to know how useful this approach to C-peptide suppression is; it has been used in only a few patients. Furthermore, if the patient is hypoglycemic before the test, the test is virtually in progress: measurement of plasma glucose, insulin, and C-peptide will provide a diagnosis. If the patient is not hypoglycemic, the standard test (insulin infusion without glucose clamping) can be conducted. Plasma glucose responses to intravenous glucagon, whether at the end of a prolonged fast or in the postabsorptive state, provide useful diagnostic information. Blunted plasma glucose response suggests glycogen storage disease or another hepatic disorder that precludes glycogenesis or glycogenolysis. Blunted plasma glucose response at the end of a prolonged fast but normal response in the postabsorptive state indicates intact glycogenolysis and suggests impaired substrate availability.

If repeated demonstration of Whipple's triad and hyperinsulinemia during routine activities is not feasible, the patient should undergo a supervised fast. During the fast the patient should be active during the day and may consume noncaloric beverages. The frequency of blood sampling is influenced by the patient's history of tolerance to food withdrawal (e.g., every six hours) and may be increased (e.g., every one to two hours) as the plasma glucose approaches the hypoglycemic range. Whenever blood is taken for glucose determination,

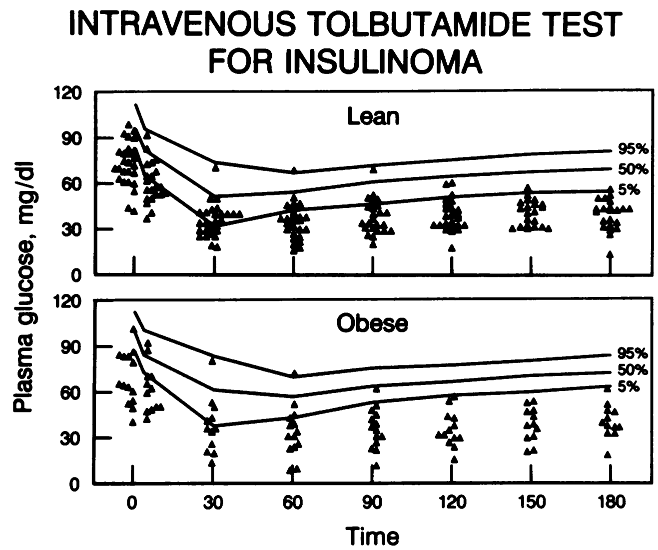

Figure 10.—The 5th, 50th, and 95th percentile plasma glucose responses to intravenous tolbutamide test are shown for lean and obese control subjects in contrast to responses (triangles) in lean and obese patients with histologically confirmed insulinoma. (Modified from McMahon MM, et al: Mayo Clin Proc 1989; 64:1481.)

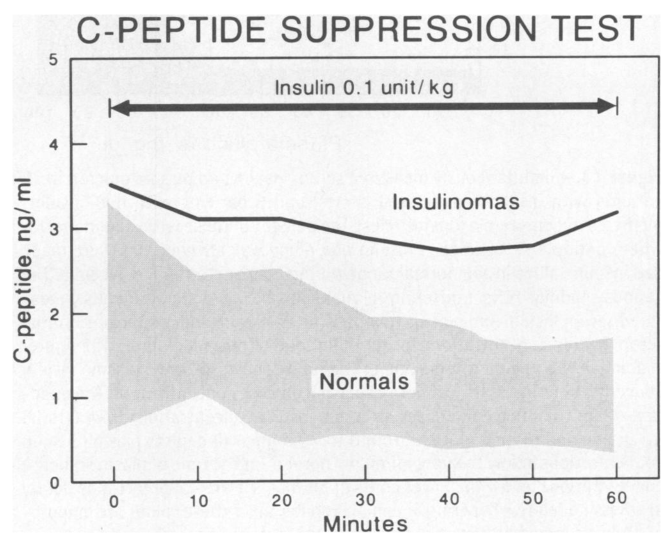

Figure 11.—C-peptide suppression test in insulinomas (M ± SEM) and controls (shaded). In response to insulin-induced hypoglycemia, insulinomas fail to suppress C-peptide. (Modified from Service FJ and Nelson RL: Insulinoma. Compr Ther 1980; 2:70.)

plasma insulin and C-peptide should also be measured. Plasma should be submitted for sulfonylurea measurement if surreptitious ingestion of this drug is suspected. The patient's intellectual status should be checked regularly by simple mathematic tasks such as serial 7s. During prolonged fasting, healthy women may experience lower plasma glucose concentrations than those noted in healthy men: values as low as the low 40s in men and mid-30s in women may be unaccompanied by symptoms.[34] Therefore, it is essential to continue the fast to the point at which symptoms develop, or to 72 hours. Upon demonstration of Whipple's triad, the fast may be terminated by the intravenous injection of glucagon, 1 mg. An increase in plasma glucose (>15 mg per dl) within 30 minutes is observed in patients whose hypoglycemia is mediated by insulin or an insulin-like factor. A blunted response is consistent with a non–insulin-mediated hypoglycemic disorder (Figure 12). Plasma insulin concentrations may be in the "normal" range in about 50% of determinations when the plasma glucose is in the hypoglycemic range; 10% to 20% of patients with insulinoma may have all insulin values in the "normal" range during hypoglycemia; however, the plasma insulin concentration is probably excessive if it is above 6 μU per ml and certainly excessive if it is above 10 μU per ml during hypoglycemia (Figure 13). Various glucose-insulin ratios provide less diagnostic accuracy.[34]

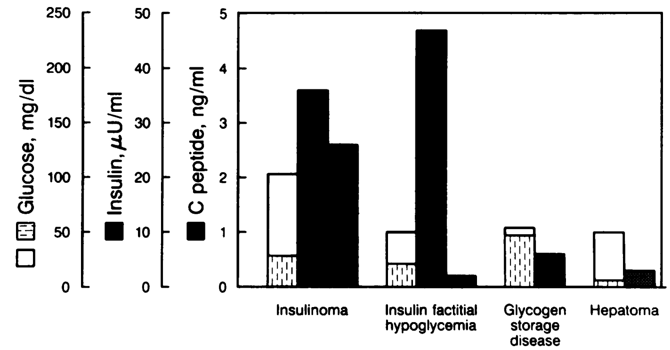

Figure 12.—Plasma glucose, insulin, and C-peptide response to intravenous injection of glucagon in the fasting state in four different types of food-deprived hypoglycemia. Insulinoma is characterized by high insulin and C-peptide levels, whereas insulin factitial hypoglycemia has high insulin but suppressed C-peptide levels; both respond normally to glucagon injection (white bar above basal glucose, hatched bar). Glycogen storage disease shows suppressed insulin levels and poor response to glucagon injection. Hepatoma shows suppressed insulin levels and normal response to glucagon; the latter is indicative of sufficient intact hepatic tissue to store and release glucose and possibly a mediation of hypoglycemia by insulin-like factors (IGFs).

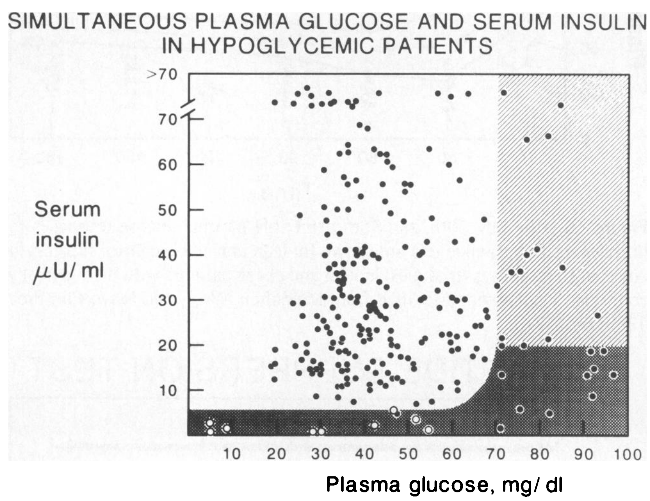

Figure 13.—Simultaneously measured serum insulin and plasma glucose in 72 patients with insulinomas (closed circles) and 6 patients with non-insulin-mediated hypoglycemia (open circles). Ten percent of those with insulinoma for whom multiple simultaneous insulin and glucose determinations were made had insulin values in the normal range during concomitant hypoglycemia. The various shadings reflect differing relationships between simultaneously measured serum insulin and plasma glucose. The darkest shading indicates normal serum insulin concentrations for the full range of plasma glucose. The lighter shading in the upper right portion of the figure shows elevated plasma insulin concentrations in the face of normal plasma glucose concentrations. The quadrant of light shading encompassing serum insulin concentrations from 6 to 25 μU per ml and plasma glucose from 0 to 70 mg per dl depicts plasma insulin concentrations below the upper limit of "normal" at the time of plasma glucose concentrations below the lower limits of normal, the area of greatest difficulty in assessing relative hyperinsulinemia. Probably all of these values are inappropriately elevated because they are above 6 μU per ml. The unshaded portion on the upper left part of the figure shows elevated serum insulin concentrations and depressed plasma glucose concentrations, all of which are consistent with the diagnosis of insulinoma. (Modified from Service FJ and Nelson RL: Insulinoma. Compr Ther 1980; 2:70.)

In a series of 95 patients with insulinoma who underwent diagnostic fasts, Whipple's triad was demonstrated within 12 hours of the last meal in 29%, within 24 hours in 71%, within 36 hours in 79%, within 48 hours in 92%, within 60 hours in 97%, and within 72 hours in 98%.[34] In rare instances, patients with insulinoma may not develop hypoglycemia during prolonged fasting of even up to 96 hours.[34,40] At the time of hypoglycemic symptoms in the group of 90 patients with insulinoma, plasma glucose concentrations were $\leq$46 mg per dl in 100%, $\leq$39 mg per dl in 70%, $\leq$35 mg per dl in 50%, and $\leq$28 mg per dl in 25%.[34]

The intravenous glucagon test has a diagnostic accuracy of 50% to 80% using criteria of peak insulin $\geq$130 μU per ml or increase above basal $\geq$100 μU per ml when conducted after an overnight fast.[41] Hydrochlorothiazide, diphenylhydantoin, and diazoxide may give false-negative responses; tolbutamide, aminophylline, and obesity may give false-positive results.[41] The utility of other tests such as glycosylated hemoglobin, human pancreatic polypeptide, and infusions of alcohol, calcium, epinephrine and propranolol, diazoxide, and somatostatin-tolbutamide in the diagnosis of insulinoma is unproved or inadequate. Human chorionic gonadotropin or one of its subunits may be a marker for functioning malignant insulinomas.[42] Eighty percent of patients with insulinoma may have elevated proinsulin concentrations (>20% of total immunoreactive insulin).[43] Perhaps proinsulin measurements with more modern assays may improve diagnostic accuracy, but these assays are not generally available. In most instances the evaluation of a patient with insulinoma yields unequivocally positive results. On some occasions, however, the data are borderline or even contradictory. In order to make one's way to the correct diagnosis, the reliability of the data needs to be rechecked, the conditions under which they were collected must be ascertained to be proper, and additional corroborating data must be generated.

Localization. Only after the diagnosis of insulinoma has been confirmed biochemically should a localization procedure be done. Pancreatic angiography has been reported to have a high rate of success when stereoscopy, magnification, and subtraction are used[44] (Figure 14). Insulinomas appear as homogeneous, intensely vascular, sharply circumscribed masses within the substance of the pancreas.

Computed tomography has had limited success in localization (Figure 15). Real-time high-resolution ultrasonography done both preoperatively and intraoperatively is currently demonstrating a high degree of accuracy. In a large series of patients with solitary insulinomas, preoperative ultrasonography successfully localized 63% of the tumors and intraoperative ultrasonography localized 86%[45] (Figure 16). The indications for and value of selective venous sampling for insulin measurement done either by the percutaneous transhepatic route or directly at the time of surgery remain undetermined. Failure to localize an insulinoma should not deter pancreatic exploration in a patient for whom the diagnosis has been firmly established. Surgeons experienced in insulinoma surgery are highly successful in finding the tumor even when it has not been localized preoperatively.[46]

Treatment. Surgical removal is the preferred form of treatment for insulinoma. In a series of 95 patients with insulinoma, 54% of patients underwent successful enucleation of the tumor, 38% partial pancreatectomy, and the remainder a variety of other procedures.[34] In this series, 84% were cured, 7% had diabetes, and the remainder required medical treatment to control persistent hypoglycemia from malignant insulinoma, islet hyperplasia, or a tumor missed during surgery. There was no operative mortality, and the postoperative complication rate was 10%.[34]

Intraoperative glucose monitoring should not be relied upon for surgical management, since there is a high incidence of failure of plasma glucose to increase shortly after successful insulinoma removal.

The median diameter of benign tumors has been reported to be 1.5 cm.[34] Malignant tumors are usually large. Tumors are evenly distributed throughout the pancreas whether benign or malignant, single or multiple. Ectopically located insulinoma and islet hyperplasia are quite rare.[34] The latter is a difficult histologic diagnosis to make and requires quantitative techniques for the establishment of islet number and volume.[47] There is no correlation between the severity of symptoms and size of the insulinoma.[34] Insulinomas have been classified on the basis of the number and type of secretory granules[48] and functional status. Hyperinsulinism from insulinoma appears to be due not to overproduction of insulin but probably to a defect in storage of insulin. Agranular tumors have the highest concentrations of proinsulin.

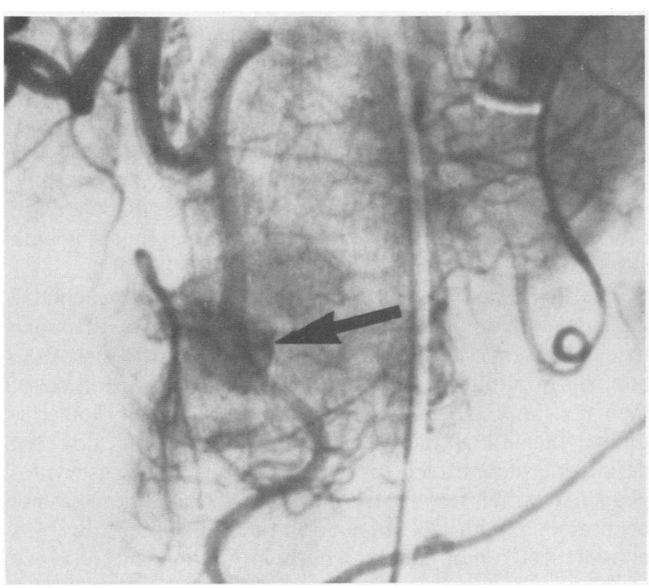

Figure 14.—Celiac axis angiogram: hypervascular tumor **(black arrow)** in the head of the pancreas. (From Stephens DH: Pancreas: Neoplastic lesions, *In* Margulis AR, Burhenne HJ (Eds): Alimentary Tract Radiology, Vol 4. St. Louis, CV Mosby, 1989.)

Treatment of persistent hypoglycemia in a patient with malignant insulinoma, in a patient in whom insulinoma cannot be found at pancreatic exploration, or in one who refuses surgery is best accomplished with diazoxide,[49] which inhibits insulin release, although phenytoin, propranolol, and verapamil have been used successfully in some cases. Long-acting somatostatin analogue has proved useful to control hypoglycemia in some patients with malignant insulinoma. Malignant insulinoma metastasizes primarily to local structures such as regional lymph nodes and liver; distant metastases are uncommon.[50] The chemotherapeutic regimen of choice consists of streptozotocin and 5-fluorouracil.[51] Survival exceeds that recorded for adenocarcinoma of the pancreas.

Factitial and Autoimmune Hypoglycemia

The self-administration of insulin or sulfonylurea may be done covertly by persons with or without diabetes, or these drugs may be administered to an unsuspecting victim or by error.

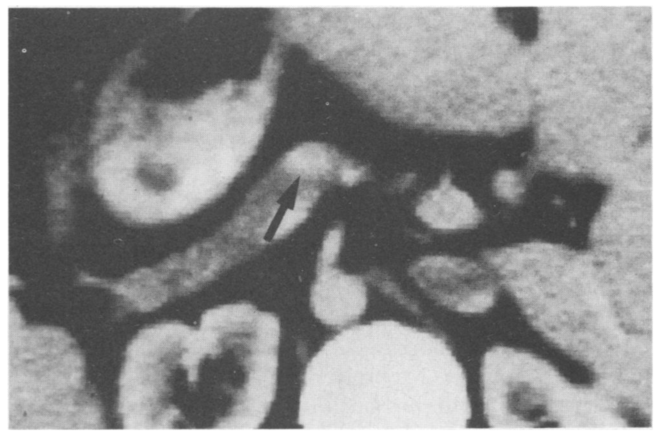

Figure 15.—Computed tomography scan of the pancreas showing an enhancing tumor **(black arrow).** (From Stephens DH: Pancreas: Neoplastic lesions, *In* Margulis AR, Burhenne HJ (Eds): Alimentary Tract Radiology, Vol 4. St. Louis, CV Mosby, 1989.)

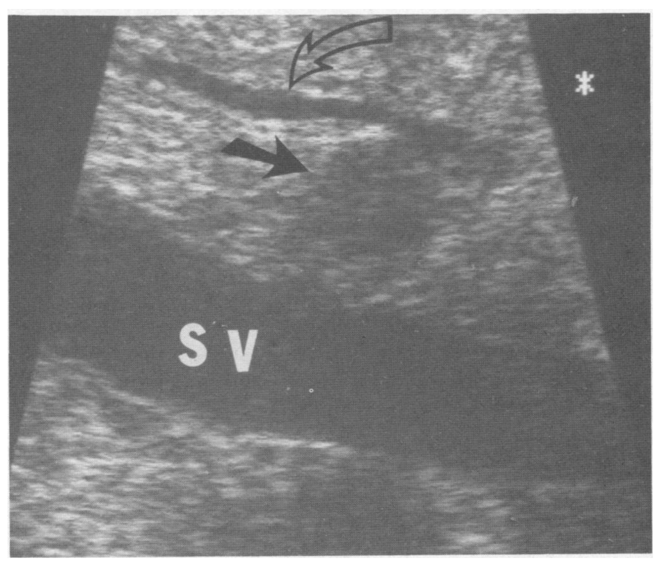

Figure 16.—Intraoperative sonogram showing a 0.8 cm discrete hypoechoic lesion **(black arrow)** within the pancreas between the main pancreatic duct **(open arrow)** and splenic vein **(SV).** (From Gorman B, Charbonneau JW, James ME, et al: Benign pancreatic insulinoma: Preoperative and intraoperative sonographic localization. AJR 1986; 147:929.)

Nondiabetic persons who secretly take insulin or sulfonylureas are predominantly women in the third and fourth decades of life who are employed in health-related occupations.[52] Patients with factitial hypoglycemia have an erratic pattern to the occurrence of symptoms and may tolerate prolonged periods of food deprivation without developing hypoglycemia. With the exception of the unusual cases of insulin autoimmune syndrome and rare detection in insulinomas, the presence of insulin antibodies is strong evidence of repeated injection of insulin. In addition, the presence of low plasma concentrations of C-peptide concomitant with elevated insulin levels and hypoglycemia indicates an exogenous source of insulin (see Figure 12). Insulin antibodies will result in spurious radioimmunoassayable plasma insulin concentrations: very high if the double antibody assay is used and undetectable if the charcoal-coated dextran assay is used. Results of tests for insulinoma (including the C-peptide suppression test if the patient is taking a sulfonylurea)[53] may be indistinguishable between an insulinoma patient and a patient who secretly took the hypoglycemic agent before the test. Concentrations of sulfonylurea should be measured in the plasma or urine if it is suspected of being the hypoglycemic agent. The clinical pattern in diabetic subjects consists of increased frequency of hypoglycemia during treatment and persistence of hypoglycemic episodes after apparent cessation of use of the agent. The presence of insulin antibodies is of no help in the diagnosis in the insulin-treated patient. The rule for the nondiabetic person, that an inverse relationship between C-peptide and insulin levels during hypoglycemia is diagnostic of surreptitious insulin administration, also holds for diabetic patients. If the diabetic patient is deprived of access to the hypoglycemic agent, such as during procedures that require immobilization of both arms or strict confinement to bed or to a seclusion room, hyperglycemia and possibly ketonuria will develop. Insulin has been used for suicide, homicide, and child abuse and by drug addicts. Accidental ingestion of a sulfonylurea has occurred as a result of errors by the patient or by pharmacy or hospital staff.

Autoimmune hypoglycemia comprises two classes of patients, those with insulin antibodies who have apparently never been exposed to exogenous insulin and those with insulin receptor antibodies. The patients with spontaneous generation of insulin antibodies have ranged in age from a few days old to elderly.[54,55] Hypoglycemia may be severe, may occur during fasting or postprandially, and is often self-limited. During episodes of hypoglycemia, plasma free insulin levels have been found to be elevated and plasma free C-peptide concentrations appear to be appropriately suppressed.[56] Distinguishing between insulin antibody autoimmune hypoglycemia and factitial hypoglycemia may be quite difficult. The observation of intermittent production of an abnormal insulin that is immunogenic[57] has not been supported by others.[58] Species-specificity association constants and binding capacities for human, porcine, and bovine insulins of the antibodies from patients with autoimmune hypoglycemia are not different from those of antibodies from insulin-treated diabetics.[56] However, there are sufficient differences in the frequency and duration of insulin administration between patients with factitial hypoglycemia and insulin-treated diabetes to require full characterization of the insulin, proinsulin, and C-peptide antibodies in proven factitial hypoglycemia for comparison with those of the autoimmune hypoglycemic syndrome.[59] Distinction between autoimmune and factitial hypoglycemia by antibody characteristics may become even more difficult now that human insulin has come into common usage. Neither the biochemical characteristics of this syndrome nor the mechanism of the hypoglycemia has been fully elucidated.

Hypoglycemia has been observed in persons with insulin receptor antibodies.[60] During the insulin resistance phase, glucose production rate is excessive and glucose utilization rate is also increased rather than decreased.[61] There are no data on glucose kinetics during the hypoglycemic phase of the disease. Most but not all of the patients with hypoglycemia had preexisting insulin-resistant diabetes and evidence for autoimmune disease before the development of hypoglycemia. Antagonist and agonist action of insulin receptor antibodies may be due to different populations of insulin receptor antibodies that recognize different antigenic sites.[62] This syndrome may respond to glucocorticoid therapy[60] or methyl palmoxinate, an inhibitor of free fatty acid oxidation,[61] but is not corrected by immunosuppressive agents or plasmapheresis.[60]

Non-Beta Cell Tumor Hypoglycemia

A wide variety of tumors of mesenchymal or epithelial origin and some malignant hematologic diseases have been associated with hypoglycemia.[63]

Mesenchymal tumors account for 45% to 64% of the reported cases. Fibrosarcomas, lymphosarcomas, liposarcoma, rhabdomyosarcomas, hemangiopericytomas, leiomyosarcomas, and mesotheliomas constitute the histologic types. The incidence is similar for both sexes. Most tumors occur in the fifth through seventh decades, although they have been observed in the pediatric age range. Tumors associated with hypoglycemia seem to have a predominantly spindle cell morphology. Approximately one third of the tumors are located in the chest and two thirds are in the abdomen, usually in the retroperitoneum. They usually are large and therefore readily detectable.

Hepatomas account for 22% of cases; they are the commonest epithelial tumor to cause hypoglycemia. The incidence of tumor-associated hypoglycemia is greater among Chinese than occidentals. There appear to be two distinct clinicopathologic types: type A is associated with rapidly growing, poorly differentiated cancers in which hypoglycemia is a preterminal event, and type B is associated with well-differentiated and more slowly growing neoplasm in which hypoglycemia occurs early in the course of the disease.[64]

Large adrenal tumors, whether functional or not, may cause hypoglycemia. Hypoglycemia has been associated in rare instances with many other tumor types but not with carcinoma of the lung.

No single pathogenetic mechanism satisfactorily explains all cases of tumor-related hypoglycemia. More than one mechanism may be involved. Metastatic destruction of the adrenals or pituitary and extensive metastatic involvement of the liver can impair glucoregulatory mechanisms. Some tumors evince a high rate of glucose utilization[16] because of a deficient Pasteur effect. In others, substances such as tryptophan metabolites may impair gluconeogenesis. There has not been a convincing documentation of insulin secretion by a non-islet cell tumor, although hyperinsulinemia has resolved after tumor removal in some cases. Although elevated concentrations of insulin-like growth factors (IGFs) have been observed in some patients with non-islet tumor hypoglycemia, there is controversy regarding their role in the pathogenesis of the hypoglycemia. The observation that plasma glucose responds to injection of glucagon in hepatoma with hypoglycemia implicates an IGF in the genesis of the hypoglycemia.[65] Proliferation of insulin receptors in insulin-responsive tissues has been reported in one patient with nonislet tumor hypoglycemia.[66] Total or partial surgical removal of the tumor usually results in amelioration of the hypoglycemia.

Hypoglycemia in Hepatic, Renal, and Endocrine Disorders and Miscellaneous Conditions

Symptomatic hypoglycemia is uncommon in liver disease because glucose homeostasis can be maintained with as little as 20% of healthy parenchymal cells, but biochemical hypoglycemia has been reported in a wide variety of acquired hepatic diseases.[67] Abnormalities of the catabolism of many glucoregulatory hormones have been observed in liver disease: glucagon, growth hormone, and cortisol, which would be expected to result in glucose intolerance but not hypoglycemia. During hypoglycemia, plasma insulin concentrations are usually appropriately suppressed. However, hyperinsulinemia may be observed as a result of impaired insulin degradation and/or shunting of portal blood into the systemic circulation. The hypoglycemia of congestive heart failure, sepsis, lactic acidosis, and Reye's syndrome is considered to be due to hepatic mechanisms.

Hypoglycemia is uncommon in adrenocortical insufficiency.[67] Hypoglycemia in hypopituitarism is common in children under six years of age but less so beyond that age.[67] Asymptomatic hypoglycemia has been observed in isolated growth hormone deficiency after prolonged fasting. Spontaneous hypoglycemia has been reported to be a frequent finding in isolated ACTH deficiency. Adults surgically deprived of epinephrine are not subject to hypoglycemia.

Hypoglycemia in nondiabetic persons with renal failure may be due to inadequate gluconeogenic substrate availability.[68] Glucagon deficiency is a theoretic mechanism for hypoglycemia, but the existence of this disorder has not been confirmed.

Hypoglycemia is a concomitant of starvation. It has been observed in persons with protein-calorie malnutrition as a result of anorexia nervosa or extreme food faddism. Inanition may be one of several factors in the genesis of hypoglycemia in patients with multisystem disease and prolonged intravenous fluid therapy. Prolonged, severe exercise may provoke hypoglycemia in untrained persons but is less likely to do so in trained athletes.

Summary

Low plasma glucose concentrations that may or may not be sufficiently low to result in symptoms can be observed as a concomitant of several diverse diseases. Treatment of the primary underlying disorder usually alleviates the hypoglycemia. For patients whose primary symptom is that of hypoglycemia, it is essential to confirm that the plasma glucose concentration is low during the occurrence of symptoms. Symptoms that occur after meals usually are mild and rarely signify serious disease. With rare exceptions, hypoglycemia resulting in major symptoms occurs in the food-deprived state. Lower concentrations of plasma insulin and C-peptide and a concomitant low plasma glucose are major clues to a correct diagnosis.

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